THE INVISIBLE OCULAR MAP*

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MANY ocular diseases occur in highly specific localities, often in select vertical, horizontal, or proximodistal (circular) distributions. Recent research has pointed to an invisible ocular map in the embryo which, like the distributions of disease, has certain features peculiar to the vertical, horizontal, and proximodistal axes. This paper discusses the invisible ocular map and raises the possibility that it may be related to the maps that are found in ocular pathology.

Ocular diseases which predominate along the horizontal axis of the eye include band keratopathy, pterygium, pinguecula, ochronosis, and trichinosis, which tend to affect the 3 and 9 o'clock positions of the corneal limbus during their initial manifestations. Trachoma and limbal vernal conjunctivitis affect the superior limbus and lid, while inclusion body conjunctivitis affects the lower lid.[1-3] Astigmatism tends mainly to predominate along either the vertical or the horizontal axis of the cornea. Other diseases occur in a circular distribution. Thus, some retinal diseases affect the retinal periphery, others the macula; sometimes uveitis strikes anteriorly, at other times posteriorly. Retinitis pigmentosa may occur in an annular distribution around the macula. Corneal degenerations tend to lie peripherally, dystrophies centrally. Streptococcal ulcerations of the cornea tend to localize centrally, staphylococcal infections more peripherally. Crystalline dystrophy—a rare hereditary condition—forms a ring around the central cornea.[3]

The mechanisms underlying these peculiar distributions remain, for the most part, obscure. Does the visual system contain a hidden map, such that broad areas of seemingly identical histological appearance have submicroscopic, point-to-point, map-like differences?

In general, there has been a tendency to account for such vertical-

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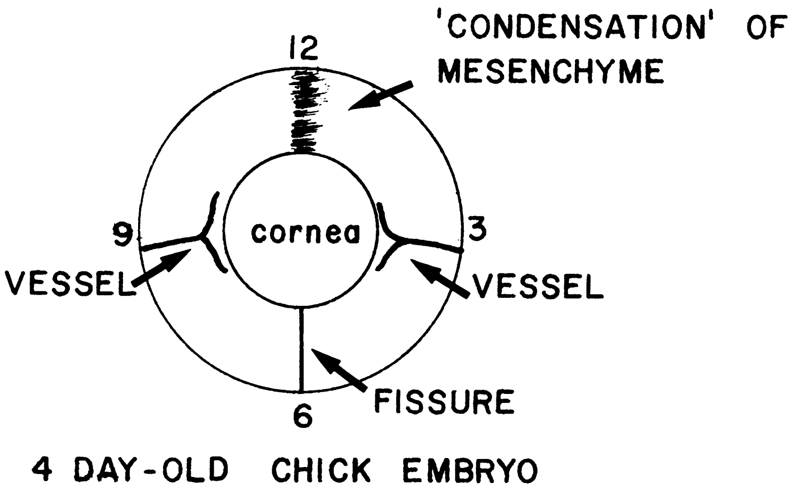

Fig. 1. Schematic drawing of the eye of a four-day-old chick.

horizontal or circular localizations of disease in terms of a diversity of unrelated mechanisms, particularly implicating the extraocular environment. Thus, pterygium occurs, it is explained, because of greater "exposure" of this particular area of the eye to unfavorable climatic conditions—but why does it occur nasally more often than temporally? Foveal diseases are said to occur because of greater exposure of the fovea to light. The 12 o'clock position of the anterior chamber angle is said to be shallowest because the upper lid presses upon the cornea. Whereas there is at present no disproof of this diversity of explanations, it should be noted that many other features of the eye demonstrate similar anatomical peculiarities, the determination of which cannot be readily explained by environmental factors. For instance:

1) In the eye of the four-day-old embryonal chick two vessels approach the cornea at 3 and 9 o'clock, the optic fissure lies inferiorly, and a condensation of mesenchyme lies at 12 o'clock (Figure 1).

2) The layering of collagen fibers in the avian corneal stroma consists of an orthogonal gridwork aligned during initial development along the nasotemporal and superoinferior axes of the eye.[4]

3) Various lower vertebrates have pigment spots on the iris at 12 and 6 o'clock or 9 and 3 o'clock.[5]

4) Only the 12 o'clock position of the iris will regenerate a new lens in the salamander.[6]

5) Growing optic fibers, on reaching the brain in the chick embryo, follow an orthogonal gridwork of other fibers arranged across the vertical and horizontal axes of the optic tectum.[7]

6) In man the anterior ciliary vessels occupy the 12, 6, 9, and 3 o'clock positions along with the four rectus muscles. The two ciliary nerves lie at 9 and 3 o'clock.[8]

7) The human retina is divided grossly into four quadrants by an imaginary vertical and horizontal line passing through the fovea. The retinal raphe is horizontal; the fovea splits vertically at the chiasm (horizontally in some animals which form a medial and lateral optic tract) and horizontally within the visual cortex at the calcarine fissure. Defects of the neurologic visual field in man tend to be quadrantic or hemianopic. The four groups of retinal vessels and four vortical veins divide the eye into four quadrants, separated by the vertical and horizontal axes of the eye.[9]

The external environment is an improbable determinant of such distributions, nor could the external body environment be responsible for those embryologically determined features which follow a circular or a radial distribution. What attracts the optic axons toward the optic stalk during development? Is there a hidden circular chemotactic gradient of some sort extending from disc to retinal periphery? What embryonic mechanisms determine the position of the macula?

Recent evidence for the existence of a hidden map within the retina has come from experiments on frogs, salamanders, and fish—which can regenerate their optic nerves. This research may be summarized as follows:

The retina connects with the brain in a highly orderly point-to-point, map-like fashion. The severing of the optic nerve in frogs, salamanders, or fish and then mixing and misdirecting of the nerve fibers results in the return of the optic fibers to their original loci, with recovery of normal function and restoration of the orderly retinotopic projection.[10-16] These experiments indicate that the optic fibers, while histologically similar, possess unseen (presumably biochemical) differences which enable them to select precisely localized points within the brain. Presumably, the bodies of the retinal ganglion cells, which are connected to the axons, also possess these differences despite the fact that ganglion cells may appear grossly similar in histological detail in various zones of the retina.

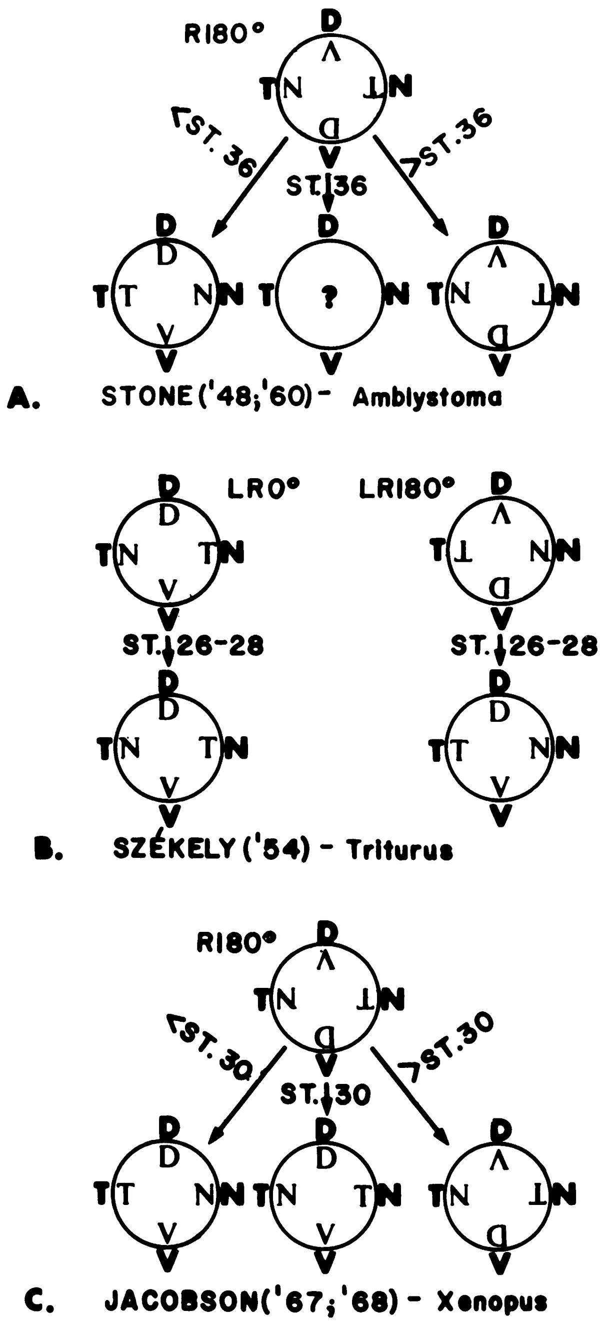

Fig. 2. Summary of experiments on ocular rotation by Stone, Székely, and Jacobson (dates are given in parentheses). Circle represents the eye. Letters placed outside the eye show the polarity of the host. Letters inside the eye show the polarity of the graft. Arrows show retinal polarity observed after operations at the stages indicated. N = nasal, T = temporal, D = dorsal, V = ventral, ST = stage, R = right eye rotations, LR = left-to-right transplants.

The physiologic basis of this invisible retinal map has remained obscure. While we know little about the *mechanisms* involved, some of the *rules* concerning the development of the map have emerged from the work of Stone, Székely, and Jacobson. These rules include certain peculiarities of the vertical and horizontal axes of the retina.

In 1948 Stone [17, 18] reported that 180° rotations of the optic vesicle of the developing eye in the salamander *Amblystoma* after embryonic stage 36 later resulted in the establishment of visual reflexes that were reversed 180°. Rotations performed before stage 36 resulted in animals with normal visual behavior. Rotations during the intermediate or critical stage 36 resulted in confused behavior. If it is assumed that this behavioral criterion reflected the state of the retinotectal connections between retina and brain, the experiments allow the inference that the eye prior to stage 36 either did not yet contain the information for polarity or contained it in reversible form. After stage 36 such information as to the polarity of the map became fixed irreversibly, i.e., determined or specified within the eye.

In 1954 Székely extended Stone's behavioral experiments to the salamander *Triturus* and made an important new finding. He reported[19] that the horizontal (nasotemporal) axis of the eye became fixed before the vertical (superoinferior or dorsoventral) axis. His experiments involved transplantation of the optic vesicle to the contralateral orbital region, with or without rotation of the vertical axis, and subsequent behavioral observation. At the stages selected for operation the horizontal axis behaved as if it were already fixed in its polarity while the vertical axis was unfixed. Székely's experiments thereby gave evidence for a separate temporal specification of the vertical and horizontal axes of the retina.

These experiments were later continued by Jacobson,[20, 21] using elegant electrophysiological recording techniques. Jacobson rotated the optic vesicle of the frog *Xenopus* 180° at various stages of development. Rotations performed prior to stage 30 were followed by normal retinotectal projection, whereas rotations done after stage 30 resulted in 180° rotation of the visual axes. Rotations performed *at* stage 30 resulted in inversion only of the horizontal retinal axis, the vertical axis being undetermined at this critical intermediate stage (sse summary in Figure 2).

From these experiments have emerged the idea of a Cartesian co-

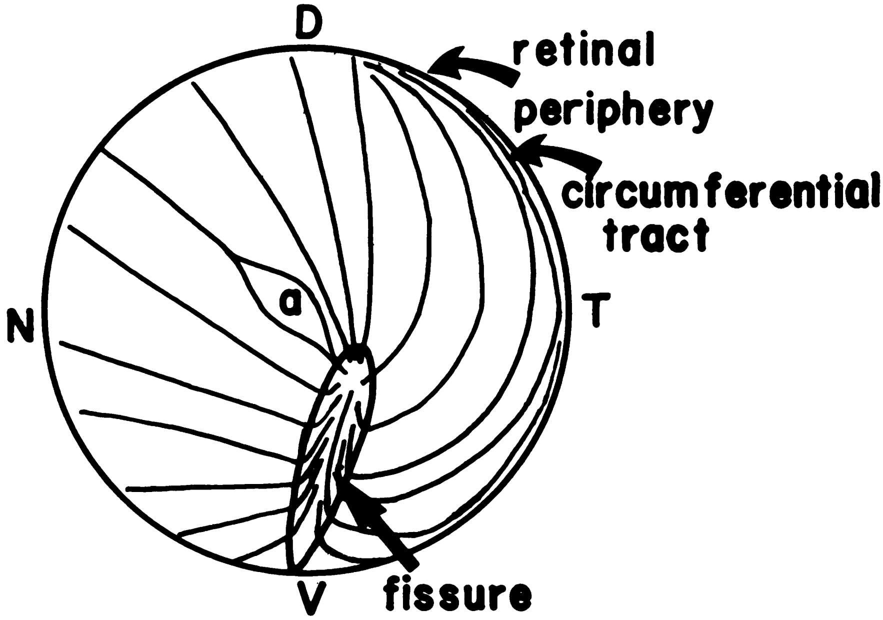

Fig. 3. Schematic view of a whole mount of a left retina. a = arcuate bundle, N = nasal, T = temporal, D = dorsal, V = ventral.

ordinate system controlling the positional information of the retinal elements. The system has features peculiar to the vertical and horizontal axes in that in some animals the horizontal retinal axis becomes fixed prior to the vertical axis.

The mechanisms underlying these phenomena have remained obscure. At first it was thought that the unspecified state meant that the very early optic vesicle might not possess the information for the retinotectal projection. Hunt and Jacobson[22] later disproved this opinion. They showed that even in the earliest phases of development the optic vesicle contains the necessary information; what happens during "fixation" is that the eye loses the ability to reverse its original polarity.

The phenomenon of separate specification of the horizontal and vertical axes probably has broad-range embryological significance, since comparable experiments (which yield similar results) have been performed on the limb,[23] ear,[24] and other structures,[25] morphological criteria of polarity were used. For instance, rotating a right limb bud 180° during the stage in which the vertical axis alone is unspecified

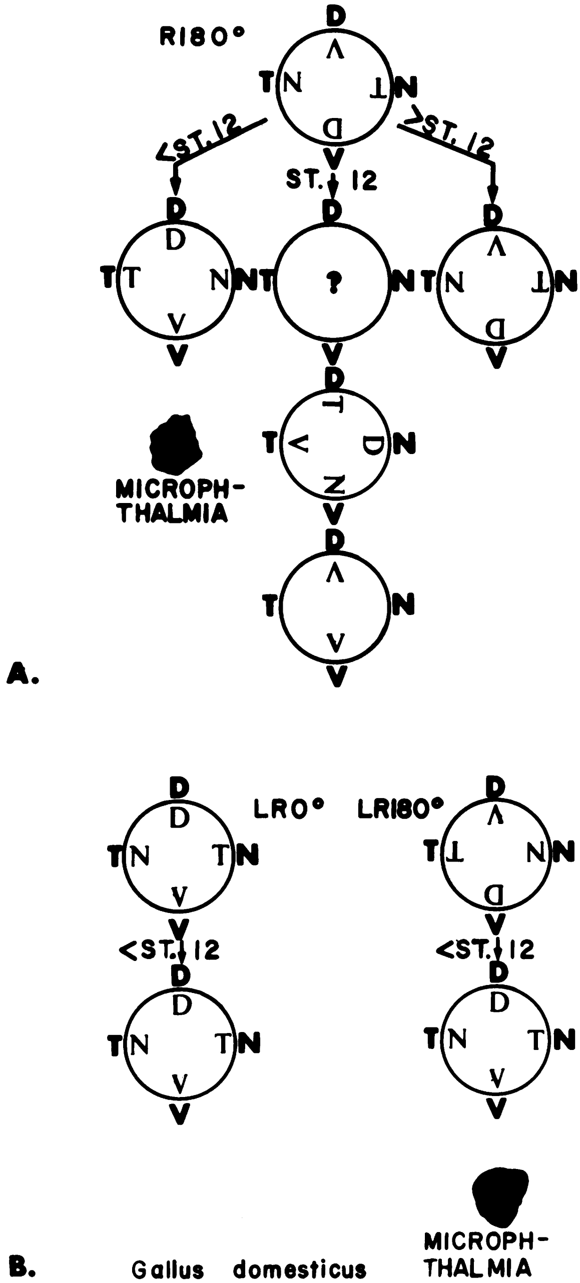

Fig. 4. Summary of results in the chick embryo following (A) right eye rotations (R) of 180° and (B) left-to-right transplantations (LR) of 0° or 180°. Operations performed before stage 12 resulted in normal patterns or severe microphthalmia. Operations done precisely at stage 12 resulted in confused patterns (central fissures), horizontal fissures, and double fissures. Operations done after stage 12 resulted in inversion of the retina. LR 0° procedures done before stage 12 resulted in no change of polarity. LR 180° rotations resulted either in severe microphathalmia or in the progressive rerotation of the axes so as to align the dorsal-ventral axis. Symbols are the same as in Figure 2.

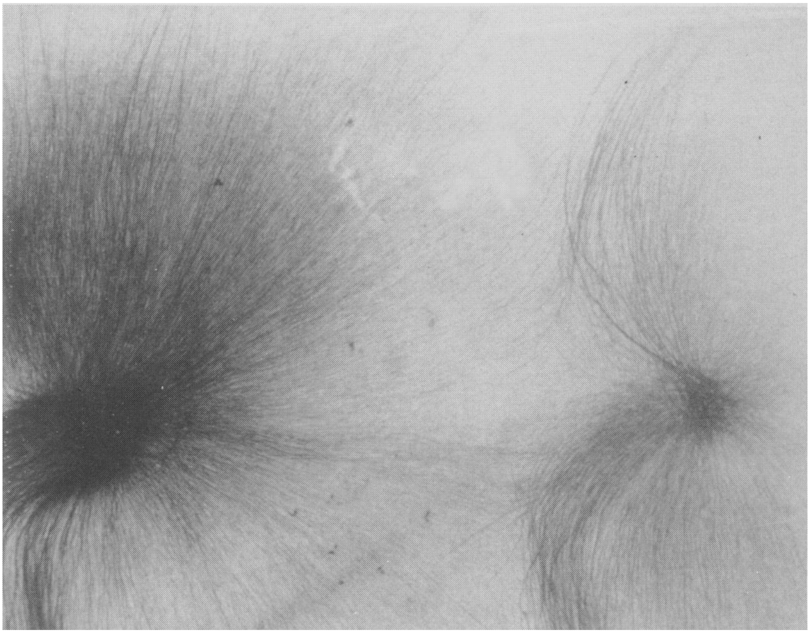

Fig. 5. Double optic nerve head following 180° rotation of the optic vesicle at stage 12.

resulted in a morphological left limb.[23] It appears probable that similar mechanisms are operating in many areas of the body and may reflect the existence of a central mechanism controlling positional information throughout the body. Studies performed with heterotopic transplants have supported the concept of a system of polarity pervading the body. Primordia of limbs,[23] ears,[24] or eyes[26] can be transplanted even to foreign areas of the body; the resultant phenomena are identical with those which occur in transplants. Thus, eyes transplanted to the flank, when rotated early enough, become eyes with normal polarity.[26] Foreign regions of the body apparently can influence ocular polarity.

Recently, the problem of retinal polarization has been approached by means of morphological techniques.[27] In 1972 Coulombre and I[28] reported that the pattern of the optic fibers in the retina of the embryonal chick presents certain morphological features, as seen in silver-stained whole mounts,[28, 29] which readily enable one to determine morphological polarity (Figure 3). With this in mind, eye transplants similar to those of the previous investigators were performed in chick embryos. The results are summarized as follows (see also Figure 4):

When the right optic vesicle of the chick embryo was removed prior to Hamburger-Hamilton stage 12 (about 45 hours of development) and reimplanted with 180° rotation of the horizontal (nasotemporal) and vertical (dorsoventral) axes, the resultant retinal morphology at seven to eight days of development was normal. Rotation performed after stage 12 produced a 180° rotated right retina. Rotation at stage 12 produced a high percentage of confused patterns, including central fissures (optic nerve heads) with indeterminate polarity, double fissures (Figure 5), and fissures at positions other than 6 and 12 o'clock. Stage 12, therefore, appeared to be critical in the fixation of morphological polarity in the retina.

When left-to-right ocular transplantations were performed before stage 12, with or without rotation of the vertical axis of the eye, sinistral retinas developed with normally oriented vertical axes (Figure 4). These experiments suggested that the process of "regulation" of polarity consists of some sort of rerotation actively driven by the vertical axis. After misalignments performed before stage 12, the vertical axis of the eye has a greater tendency than the horizontal axis to realign its position.

In further experiments the proximodistal axis of the eye was rotated so that the optic stalk pointed laterally. A progressive return of the vesicle to normal position occurred during the next four to 24 hours, provided the operation had been done prior to stages 14 to 15. In summary, the results suggested that the three major axes of the eye sequentially lose their ability to return to alignment. During these experiments the horizontal axis was never found to possess this ability; the vertical axis lost it at stage 12, and the proximodistal axis could still rerotate after stage 12. These and other experiments were elaborated further in a recent paper.[27] It also has been found that the so-called critical stage 12 is in fact variable, depending on such factors as the size and shape of the graft.

It is clear that more direct experiments are necessary to clarify the physiological bases of these phenomena and their possible relation to patterns of disease. It is of interest that the work on ocular transplantation in the chick embryo reveals much higher morbidity in grafts performed with the vertical axis rotated 180° than in unrotated grafts (Figure 4). This is difficult to explain, for in any left-to-right graft one axis, by definition, must be aligned perfectly and the other 180°

misaligned. For some reason, misalignment of the vertical axis before stage 12 usually resulted in marked distortion and microphthalmia. This was not found with misalignment of the horizontal axis. This observation may have relevance to corneal transplantation in man. Corneal surgeons in general pay no attention to clockwise orientation of corneal grafts. No effort is made to align the 12 o'clock position of the donor with that of the host. Do the phenomena observed in the chick embryo occur to some extent in the adult human in such a manner that improperly aligned corneal transplants may yield a higher incidence of astigmatism and graft failure? This question deserves further exploration.

Summary

Various ocular diseases occur in peculiar vertical, horizontal, or proximodistal distributions. Recent evidence points to the existence of a hidden map within the embryo, which also has features peculiar to the vertical, horizontal, and proximodistal axes. This map may be associated with a coordinate system responsible for the positioning of the various regions of the eye. If the embryonic map relates to the maps in ocular disease this could provide new insight into diseases which strike in selected geometric patterns.

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